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June 6, 2007

Roger Citron, RPh
Montana DPHHS
Mountain Pacific Quality Health Foundation
3404 Cooney Drive
Helena, MT 59620

Dear Mr. Citron:

We are responding to your request for clinical information for the upcoming review of the Long-acting Narcotics category at the June 27, 2007 State of Montana Drug Utilization Review Board/Formulary Committee meeting for recommendations to the Montana Medicaid Preferred Drug List. Enclosed for your review, are the following sections of OxyContin® (oxycodone HCl controlled-release) Tablets AMCP dossier that have been updated and recent information pertaining to OxyContin:

- Section 2.0 Supporting Clinical and Economic Information
  - Section 2.2: Published and Unpublished Clinical Studies
  - Section 2.4: Outcomes Studies and Economic Evaluation Supporting Data

- Section 5.0 Supporting Information
  - Section 5.1 References

We do request that this information be removed from your website once the review period ends (after the June 27, 2007 Drug Utilization Review Board/Formulary Committee meeting).

If further information is required, please contact me at (888) 726-7535.

Sincerely,

Nancy Crudele, PharmD
Sr. Manager, Medical Services

Encl: References

OxyContin References:

OxyContin [package insert]. Stamford, CT. Purdue Pharma L.P.

de Beer J , Winemaker MJ , Donnelly GAE , Miceli PC , Reiz JL , Harsanyi Z , Payne LW, Darke AC. Efficacy and safety of controlled-release oxycodone and standard therapies for postoperative pain after knee or hip replacement. *Can J Surg.* 2005;48(4):277-83.

Illgen RL, Pellino RA, Gordon DB, Butts S, Heiner JP. Prospective analysis of a novel long-acting oral opioid analgesic regimen for pain control after total hip and knee arthroplasty. *J Arthroplasty.* 2006;21(6):815-820.

Hartung DM, Middleton L, Haxby DG, Koder M, Ketchum LK, Chou R. Rates of Adverse Events of Long-Acting Opioids in a State Medicaid Program. *Ann Pharmacother.* 2007;41: 921-928.

Marshall et al. Economic Evaluation of Controlled-release Oxycodone vs Oxycodone-Acetaminophen for Osteoarthritis Pain of the Hip or Knee. *Am J Manag Care.* 2006;12:205-214.

SECTION 2.2: PUBLISHED AND UNPUBLISHED CLINICAL STUDIES

Prospective Studies in Patients with Postoperative Pain

Two separate (Phase I and Phase II), 3-week, open-label group studies evaluated pain intensity, pain relief, length of hospital stay, analgesic use and side effects following administration of OxyContin® (n = 70) and standard therapy (ST) (n = 101) for postoperative pain 48 hours after primary knee and hip replacement (de Beer J et al, [Table 24]). Phase I examined treatment with OxyContin and Phase II examined treatment with standard analgesic therapy. Patients scheduled to undergo elective primary unilateral total knee or hip replacement secondary to osteoarthritis and able to comply with the study protocol and complete study diaries were permitted to enter the study.

For the first 48 hours postoperatively, patients received intravenous morphine through patient-controlled (PCA) or epidural administration of a combination of morphine, fentanyl and bupivacaine. Upon discontinuation patients received only the following analgesics:

- Phase I : OxyContin 10-, 20-, and 40-mg tablets; rescue medication consisted of morphine 7.5-10 mg intramuscularly every 3-4 hours as needed for severe pain (in hospital) and acetaminophen 325-650 mg orally every 4 hours as needed (after discharge), or

- Phase II: Standard analgesics, according to physician's written orders. The most common regimen was acetaminophen plus codeine (A/C 300 mg/30 mg) 1-2 tablets orally every 3-4 hours as needed. Rescue medication was morphine IM as needed (in hospital) for severe pain and acetaminophen 325 mg as needed (after discharge). Alternative oral opioid analgesics included acetaminophen plus codeine (A/C 300 mg/15 mg) and oxycodone and acetaminophen combinations.

Phase I patients received OxyContin 30 mg as their first dose of study medication on the morning of the second day after surgery (day 2). Baseline pain levels were recorded once pain was of moderate intensity, following discontinuation of PCA or epidural analgesia. Subsequent doses of OxyContin followed a structured dose de-escalation schedule. Patients who required rescue medication within the first 12 hour period on day 2 had their OxyContin dose increased up to 40 mg every 12 hours. Then on days 4 and 5, these patients received 30 mg every 12 hours; on days 6 and 7, they received 20 mg every 12 hours; and on days 8-21, they received 10 or 20 mg every 12 hours. Patients who did not require rescue medication within the first 12-hour period on day 2, remained on a dose of 30 mg every 12 hours on days 2 and 3. Then they received 20 mg every 12 hours on days 4, 5, and 6 and 10 or 20 mg every 12 hours on days 7-21.

Phase II patients received ST after discontinuation of PCA or epidural analgesia, approximately 48 hour postoperatively. Baseline pain was recorded concomitant with the cessation of PCA or epidural administration. ST was based on physician's written orders.

Efficacy and safety evaluations were based on the patient diary and on assessments completed by patients during the first 4 hours after the first dose of study medication and during the follow-up visit. Pain intensity was assessed using a 100-mm VAS. The VAS was an unmarked line, bounded on the left by "no pain" and on the right by "excruciating pain." During the hospital stay, patients were issued a daily diary (diary 1) to complete the visual analogue and categorical scales for pain intensity and pain relief 3 times per day (morning, afternoon, and evening). In both Phase I and Phase II, the times to first rescue analgesic, the dose of rescue analgesics and the number of rescue analgesics used by each patient were also recorded, with the addition of time and type of analgesic taken recorded in Phase II.

For an additional 2 weeks after discharge, patients in Phase I recorded in the daily diary (diary 2) the number of OxyContin tablets they took and the date and time they were taken. Also patients were instructed to document the date, time and the number of acetaminophen 325 mg tablets to alleviate pain that was not controlled following the appropriate dose of OxyContin. Diary 2 contained the same visual analogue and categorical scale assessments as those in diary 1. In Phase II, patients recorded the same measures as Phase I for all analgesics taken.

In both phases, at 2 weeks postoperatively, patients were asked to complete brief pain inventory (BPI) short form. Most questions were scored on a 0-10 scale with 0 = no pain or difficulty and 10 = maximum pain or difficulty. A composite pain score (Pain Intensity) and composite functional ability score (Functional Impairment) were calculated by summing the appropriate individual items for each. In addition, a pain relief measure (% of relief afforded) and hours measure (the number of hours for which pain medications were not required) was reported.

At the time of discharge from the hospital, patients in the OxyContin group recorded lower mean [standard deviation] pain intensity scores than the ST group (20.2 [17.9] v. 27.7 [21.5] mm on a 100-mm visual analogue scale; $p = 0.021$). Length of hospital stay was 5.5 and 6.4 days for the OxyContin and ST groups, respectively ($p < 0.001$). OxyContin patients used less opioid (morphine equivalents) while in hospital than ST patients ($p < 0.001$), and the average number of daily administrations of analgesics in hospital was 2.1 and 3.5 for OxyContin and ST patients, respectively ($p < 0.001$).

Summary of the BPI at 2 weeks postoperatively found pain equally well controlled between phases, although patients displayed less functional impairment in Phase I (see Table).

Table. Summary of the Brief Pain Inventory Scores 2 Weeks Postoperatively

	Therapy; Mean (SD) Total Score	
Category	**OxyContin (Phase I)**	**Standard Therapy (Phase II)**
Pain Intensity	11.3 (6.8)	12.7 (6.6)
Functional Impairment	22.9 (13.7)	29.2 (16.2)*
Pain relief (%)	75.9 (19.1)	73.4 (24.3)
Hours between medication doses	5.6 (1.2)	5.1 (1.2)†

*p= 0.014, †p=0.013

Standard therapy patients reported more nausea and vomiting, pruritus, and fever than the OxyContin patients, but less somnolence, constipation, dizziness, confusion, and tachycardia.

Authors concluded that OxyContin every 12 hours is as effective as standard therapy in treating postoperative pain but length of hospital stay was shorter and analgesic administration in the hospital was less frequent in OxyContin treated patients, providing potential hospital cost savings and reduced use of health care resources.

Table 24 Postoperative Pain

Citation/Study Dates	Design	Inclusion Criteria	Exclusion Criteria	Power	Sample Size	Treatments	Endpoints	Results and Statistical Significance
de Beer J , Winemaker MJ , Donnelly GAE , et al. Efficacy and safety of controlled-release oxycodone and standard therapies for postoperative pain after knee or hip replacement. *Can J Surg.* 2005;48(4): 277-283.	Two separate 3-week open-label studies Phase I: Patients enrolled Sept. 1999 to Jan. 2000 Phase II: Patients enrolled Jan. 2001 to Sept. 2001	Schedule to undergo elective primary unilateral total knee or hip replacement secondary to osteoarthritis Able to comply with study protocol Able to complete study diaries.	Allergy to any opioid A history of drug abuse Ingestion of opioid analgesics within 24 hours before the operation Recipient of workers' compensation benefits Inflammatory arthritis or significant pain of other origin	Statistical significance was defined as $p<0.05$ for a two-tailed hypothesis.	Phase I: n=70 (evaluable population) Phase II: n=101 (evaluable population)	First 48 hours postop, patients received IV morphine via PCA or epidural of combination of morphine, fentanyl and bupivacaine Upon d/c, pts received: Phase I: OxyContin 10-, 20-, 40 mg tablets q12h Rescue med: morphine 7.5-10 mg IM q3-4h and APAP 325-650 mg q4h prn Phase II: standard analgesics according to physicians orders (ST) Rescue med: morphine 7.5-10 mg IM q3-4h and APAP 325-650 mg q4h prn	Pain intensity 100-mm VAS (0= no pain; 100= excruciate-ing pain) 2 weeks postop BPI short form; most questions scored on 0-10 scale (0=no pain or difficulty; 10=max pain or difficulty) Length of hospital stay Opioid analgesic dose Number of opioid admins. Adverse events coded (COSTART IV)	At the time of discharge from hospital, patients in OxyContin group recorded lower mean (and standard deviation) pain intensity scores than the ST group (20.2[17.9] vs. 27.7 [21.5] mm on 100-mm VAS ($p=0.021$). Length of hospital stay for OxyContin group was 5.5 and ST was 6.4 days for ($p=0.001$). Summary of BPI at 2 weeks postop found pain equally well controlled between phases, although patients displayed less functional impairment in Phase I. OxyContin patients used less opioid (morphine equivalents) while in hospital than ST patients ($p<0.001$). Average number of daily admin. of analgesic in hospital for OxyContin patients was 2.1 and for the ST group 3.5 ($p<0.001$). ST group reported more nausea, vomiting, pruritus and fever than OxyContin group OxyContin group reported more somnolence, constipation, dizziness, confusion, and tachycardia than ST group

Prospective Studies in Patients with Postoperative Pain

A prospective study was conducted to compare the use of traditional intravenous patient-controlled analgesia (IV PCA) versus oxycodone controlled-release (OxyContin®) in postoperative pain patients after total knee arthroplasty (TKA) or total hip arthroplasty (THA) (Illgen RL et al., 2006 [Table 27]).

One hundred and twenty four patients were included in either a preintervention design group (n= 62) or postintervention design group (n=62). Patients in the preintervention group received IV PCA either with morphine sulfate 1 to 2 mg or hydromorphone 0.2 to 0.4 mg with a 6-minute lockout for postoperative pain management between March 2001 and June 2003. Patients in the postintervention (new standardized postoperative orders) group received OxyContin 20 mg starting preoperatively the morning of surgery and continued twice daily through postoperative day 3 (6 doses total) between July and October 2003. Patients were allowed a short-acting oral opioid (oxycodone 5 to 20 mg every 3 hours) as needed. Intravenous opioids were given only if the patient did not obtain satisfactory pain control or if they developed nausea or vomiting using the oral regimen.

Outcome measures included visual analog pain scores, total opioid consumption, functional interference measures, and rates of opioid-related side effects. Patients were surveyed each day at approximately the same time for 3 days about their experiences in the past 24 hours using a survey adapted from the American Pain Society's Patient Outcome Questionnaire and the Brief Pain Inventory, and a medical record audit was completed for the same periods. Information was collected from patients' charts regarding the total amount of opioid administered, side effect management, and physical therapy tolerance.

No significant differences in any of the outcome measures tested were detected between THA and TKA groups; therefore, all data presented was the combined THA and TKA findings. Patients in both the OxyContin and IV PCA groups had similar pain ratings for all 3 days. Mean worst pain ratings were approximately 8 (range, 2-10) on postoperative day 1 and gradually decreased to a mean of 6 by day 3 in both groups (range, 0-10). There was no difference in the amount of moderate to severe pain in either group. Patients in the OxyContin group used significantly less opioid (mean parenteral morphine equivalent) in the first 24 hours after surgery than patients using IV PCA (37.80 mg $\pm$ 23.45 vs. 59.41 $\pm$ 37.00 mg, respectively, $p < 0.001$). On days 2 and 3, opioid use was similar in both groups. Twenty-six (42%) of patients in the OxyContin group received at least 1 parenteral rescue dose in the first 24 hours. By day 3, 80% of patients in the IV group had been transitioned to oral opioids on as needed basis.

Patients in the OxyContin group reported significantly less interference from pain in walking ($p = 0.024$) and coughing ($p = 0.022$) on day 1, falling asleep ($p = 0.001$), staying asleep ($p = 0.013$), coughing ($p = 0.004$), and deep breathing ($p = 0.011$) on day 2, and getting out of bed ($p = 0.05$), walking ($p = 0.038$), staying asleep ($p = 0.001$), coughing ($p = 0.003$), and deep breathing ($p = 0.003$) on day 3. No statistically significant differences were noted in length of stay for OxyContin compared to IV PCA groups. Patient satisfaction ratings reached a statistical difference by day 3 in favor of the OxyContin group versus the IV PCA group ($p < 0.05$). No statistically significant differences in side effects were reported. On all 3 days, drowsiness was most frequently reported, followed by nausea, dizziness, and itching. By day 3, constipation became a frequently reported side effect.

Table 27 Postoperative Pain

Citation/Study Dates	Design	Inclusion Criteria	Exclusion Criteria	Power	Sample Size	Treatments	Endpoints	Results and Statistical Significance
Illgen RL. Pellino TA, Gordon DB, Butts S, Heiner JP. Prospective analysis of a novel long-acting oral opioid analgesic regimen for pain control after total hip and knee arthroplasty. *J Arthroplasty.* 2006. 21(6):814-820.	Prospective, pre-intervention and post-intervention design	Postoperative THA and TKA pain patients	N/A	Power analysis performed using opioid use (parenteral mg morphine equivalency) as outcome variable Using $\alpha = 0.05$ and 1-sided analysis, 28 patients in each group would yield power or 0.80 Independent t-tests used to detect differences between IV PCA and OxyContin groups for age, pain intensity, opioid use, side effects, interference with function, satisfaction, and length of stay X^2 analysis used to test between group differences for sex, type of surgery, and amount of time in moderate to severe pain.	n = 124	Preintervention group received IV PCA either with morphine sulfate 1 to 2 mg or hydromorphone 0.2 to 0.4 mg with a 6-minute lockout for postoperative pain management between March 2001 and June 2003 Postintervention group received OxyContin 20 mg starting preoperatively the morning of surgery and continued twice daily through postoperative day 3 (6 doses total) between July and October 2003 Oxycodone 5 to 20 mg every 3 hours as needed	Visual analog pain scores Total opioid consumption Functional interference measures Rates of opioid-related side effects	No difference in the amount of moderate to severe pain in either group OxyContin group used significantly less opioid (mean parenteral morphine equivalent) in the first 24 hours after surgery than patients using IV PCA (37.80 mg $\pm$ 23.45 vs. 59.41 $\pm$ 37.00 mg, respectively, $p < 0.001$) OxyContin group reported significantly less interference from pain in walking ($p = 0.024$) and coughing ($p = 0.022$) on day 1, falling asleep ($p = 0.001$), staying asleep ($p = 0.013$), coughing ($p = 0.004$), and deep breathing ($p = 0.011$) on day 2, and getting out of bed ($p = 0.05$), walking ($p = 0.003$), staying asleep ($p = 0.001$), coughing ($p = 0.003$), and deep breathing ($p = 0.003$) on day 3 No statistically significant differences in side effects were reported

Retrospective Claims Database Study: Rates of Adverse Events of Long-Acting Opioids in a State Medicaid Program. (Hartung et al. Ann Pharmacother. 2007;41: 921-928.)

The purpose of this study was to evaluate the risk of serious adverse events among Oregon fee-for-service Medicaid recipients prescribed long-acting opioids (LAO) using a retrospective observational cohort methodology. Four cohorts were established based on the index prescription fill, defined as the first prescription claim during the study period for LAOs methadone (Dolophine and generics), ER oxycodone (OxyContin and generics), ER morphine (MS Contin, Oramorph, Kadian, Avinza, and generics), and transdermal fentanyl (Duragesic and generics).
Subjects were included if they had at least one prescription of at least 28 days' supply between January 1, 2000, and December 31, 2004, and at least 180 days of continuous Medicaid fee-for-service program eligibility prior to their first index fill. Continuous exposure was defined as successive LAO prescriptions at a maximum interval of 31 days from the last prescription's days' supply. Subjects in the ER morphine cohort were used as the reference cohort.

The primary outcome was the first administrative claim for an emergency department (ED) visit or hospitalization with a diagnostic code suggesting an opioid-related adverse event. Specifically, ED and hospitalizations with an ICD-9 diagnosis code for poisoning by opiates and related narcotics (9650x); alteration of consciousness (7800x); malaise, fatigue, or lethargy (7807x); respiratory failure (51881, 51882); or constipation (5640x) were identified. Hospitalizations were identified using the Diagnosis-Related Group coding system. The rates of all-cause ED encounters and hospitalizations, as well as encounters for opioid-related adverse events were compared between cohorts. Estimated differences in the rate of all-cause mortality were evaluated based on data from the monthly vital statistics report provided by the Oregon Center for Health Statistics.

Cox proportional hazards models were used to adjust the following covariates: age, race, sex, long-term care residence, number of unique prescribers, disease severity, concomitant prescription claims for drugs with known pharmacodynamic interactions with LAOs, the type of presumed pain diagnosis, and history of opioid dependence, abuse, or enrollment in a substance abuse treatment program. Pain diagnosis were identified using ICD-9 codes from medical encounter claims processed one year before and after a subject's cohort entry date and included osteoarthritis, back pain (dorsopathies), peripheral nervous system disorders, fibromyalgia, and neoplasm. The prevalence of opioid dependence, abuse, or enrollment in a state-monitored substance abuse program was also quantified and adjusted for. For each cohort, the average daily dose of long- and short-acting opioids was calculated and converted to a morphine-equivalent daily dose. Also quantified was whether a different LAO was started subsequent to the end of the patients' original LAO exposure (LAO change). In addition, the occurrence of outcomes in subjects with a diagnosis of cancer and those without

cancer who had a diagnosis of osteoarthritis, fibromyalgia, back pain, or neuropathy was evaluated.

Over the study period, a total of 5,684 subjects had an index prescription for an LAO with a minimum 28 days' supply, with the largest cohort prescribed oxycodone ER and the smallest prescribed methadone. Multiple statistically significant differences among the cohorts' demographics were noted (Table 1).

Table 1. Cohort Demographics

Characteristic	Transdermal Fentanyl	Methadone	ER Oxycodone	ER Morphine	p Value
N = 5684	1546	974	1866	1298	
Age, y (mean ± SD)	70.6 ± 18.1	51.1 ± 15.4	57.4 ± 17.9	58.5 ± 17.0	<0.001
Prescribers, n (mean ± SD)	2.5 ± 1.9	2.6 ± 2.4	2.6 ± 1.9	2.6 ± 2.1	0.256
Interacting drug, n (mean ± SD)	1.5 ± 1.2	1.4 ± 1.3	1.7 ± 1.3	1.5 ± 1.2	<0.001
Charlson Comorbidity Index (mean ± SD)	1.0 ± 1.7	0.9 ± 1.5	1.2 ± 1.9	1.4 ± 2.1	<0.001
Equivalent dose/day (mean ± SD)	96.0 ± 42.5	246.6 ± 310.9	66.7 ± 79.4	74.0 ± 78.5	<0.001
Short-acting opioid equivalent dose/day (mean ± SD)	4.3 ± 14.8	4.5 ± 12.2	5.8 ± 15.7	3.1 ± 7.3	<0.001
Switched LAO after follow-up, n (%)	234 (15.1)	170 (17.5)	572 (30.7)	242 (18.6)	<0.001
Female, n (%)	1144 (74.0)	615 (63.1)	1208 (64.7)	848 (65.3)	<0.001
Non-white, n (%)	95 (6.1)	102 (10.5)	143 (7.7)	125 (9.6)	<0.001
Long-term care residence, n (%)	439 (28.4)	40 (4.1)	185 (9.9)	160 (12.3)	<0.001
Non-English speaker, n (%)	25 (1.6)	15 (1.5)	21 (1.1)	25 (1.9)	0.323
Cancer, n (%)	307 (19.9)	178 (18.3)	471 (25.2)	339 (26.1)	<0.001
Osteoarthritis, n (%)	212 (13.7)	220 (22.6)	361 (19.3)	234 (18.0)	<0.001
Fibromyalgia, n (%)	73 (4.7)	176 (18.1)	185 (9.9)	118 (9.1)	<0.001
Back pain, n (%)	271 (17.5)	407 (41.8)	654 (35.0)	355 (27.3)	<0.001
Neuropathic pain, n (%)	112 (7.2)	163 (16.7)	148 (7.9)	244 (18.8)	<0.0001
Substance abuse treatment center, n (%)	19 (1.2)	86 (8.8)	68 (3.6)	46 (3.5)	<0.0001
Substance abuse, n (%)	2 (0.1)	9 (0.9)	2 (0.1)	3 (0.2)	<0.001
Substance dependence, n (%)	15 (1.0)	91 (9.3)	47 (2.5)	17 (1.3)	<0.001

ER = extended-release; LAO = long-acting opioid.

The absolute incidence of the various outcomes, as well as adjusted hazard ratios generated from multivariate Cox proportional hazards models are shown in Table 2. For the primary outcome of time to first ED or hospitalization for opioid-related adverse events, subjects in the oxycodone ER cohort were 35% less likely to have an event compared with the morphine ER cohort. Subjects in the oxycodone ER cohort were also 29% less likely to die compared to subjects in the morphine ER cohort. There were no significant differences between cohorts in the risk of any ED encounter. However, subjects prescribed methadone or oxycodone ER were significantly less likely to be hospitalized compared with morphine ER by 18% and 23%, respectively. There were no significant differences between cohorts in the risk of symptoms of overdose or the risk of being diagnosed with opioid poisoning. The diagnosis of constipation was 41% less likely in subjects prescribed oxycodone ER compared to subjects prescribed morphine ER.

Absolute risk reductions were estimated by subtracting the incidence rates for a given outcome for each cohort from the reference cohort. In absolute and unadjusted terms, subjects prescribed oxycodone ER experienced about 3.3 ED encounters or

hospitalizations for opioid-related adverse events, 8.4 ED encounters, 15.0 hospitalizations, and 8.7 deaths per 100 person years less than those prescribed morphine ER (Table 2).

A total of 1,295 subjects were identified with a cancer diagnosis (Table 3) and 2,027 had a noncancer pain diagnosis (Table 4).

Table 2. Unadjusted Incidence Rate and Adjusted Cox Proportional Hazards Model

Parameter	Events, n	Person Years	Incidence/100 Person Years	Adjusted HR	95% CI	p Value
ED encounter or hospitalization for opioid-related adverse event[a,b]						
methadone	17	473	3.6	0.71	0.39 to 1.29	0.259
oxycodone	22	909	2.4	0.45	0.26 to 0.77	0.004
fentanyl	28	779	3.6	0.73	0.44 to 1.23	0.241
morphine (referent)	31	541	5.7			
Mortality[c]						
methadone	29	476	6.1	0.71	0.46 to 1.08	0.105
oxycodone	99	912	10.9	0.71	0.54 to 0.94	0.018
fentanyl	287	785	36.5	0.80	0.63 to 1.02	0.071
morphine (referent)	107	546	19.6			
ED encounters[d]						
methadone	385	396	97.3	1.01	0.87 to 1.18	0.877
oxycodone	685	768	89.2	0.92	0.81 to 1.03	0.156
fentanyl	501	692	72.4	1.03	0.90 to 1.18	0.640
morphine (referent)	464	476	97.5			
Hospitalizations[e]						
methadone	178	404	44.0	0.82	0.68 to 0.99	0.043
oxycodone	354	788	45.0	0.77	0.66 to 0.91	0.002
fentanyl	297	697	42.6	0.93	0.79 to 1.10	0.392
morphine (referent)	276	460	60.0			
Opioid poisoning[f]						
methadone	6	475	1.3	3.22	0.60 to 17.25	0.171
oxycodone	3	910	0.3	0.87	0.14 to 5.25	0.879
fentanyl	1	789	0.1	0.46	0.04 to 5.12	0.528
morphine (referent)	2	545	0.4			
Overdose symptoms[g,h]						
methadone	113	442	25.6	1.11	0.85 to 1.44	0.455
oxycodone	167	865	19.3	0.89	0.70 to 1.13	0.324
fentanyl	135	752	17.9	0.97	0.75 to 1.24	0.778
morphine (referent)	120	516	23.3			
Constipation[i]						
methadone	22	470	4.7	0.85	0.49 to 1.48	0.559
oxycodone	28	900	3.1	0.59	0.35 to 1.00	0.049
fentanyl	27	778	3.5	0.78	0.46 to 1.33	0.361
morphine (referent)	29	535	5.4			

ED = emergency department; LAO = long-acting opioid.

[a]Adjusted for Charlson Index.

[b]Constipation, alteration of consciousness, malaise, fatigue, lethargy, respiratory failure, opioid poisoning.

[c]Adjusted for long-term care, sex, age, osteoarthritis, neuropathies, back pain, Charlson Index, number of prescribers, number of medications, short-acting opioid dose, LAO change.

[d]Adjusted for long-term care, sex, age, cancer, osteoarthritis, back pain, Charlson Index, number of prescribers, substance dependence, treatment center, dose, short-acting opioid dose, LAO change.

[e]Adjusted for long-term care, race, cancer, osteoarthritis, Charlson Index, substance abuse, short-acting opioid dose, LAO change.

[f]Adjusted for Charlson Index, number of medications, substance dependence.

[g]Adjusted for race, fibromyalgia, back pain, Charlson Index, number of medications, substance abuse, and short-acting opioid dose.

[h]Alteration of consciousness, malaise, fatigue, lethargy, respiratory failure.

[i]Adjusted for long-term care.

Table 3. Demographics of Subjects with Cancer

Parameter	Transdermal Fentanyl	Methadone	ER Oxycodone	ER Morphine	p Value
N = 1295	307	178	339	471	
Age, y (mean ± SD)	64.6 ± 16.2	52.8 ± 13.5	57.5 ± 14.9	57.0 ± 15.0	<0.001
Prescribers, n (mean ± SD)	2.9 ± 2.3	3.4 ± 3.2	2.9 ± 2.5	2.8 ± 2.1	0.037
Interacting drugs, n (mean ± SD)	1.6 ± 1.4	1.6 ± 1.4	1.7 ± 1.2	1.8 ± 1.4	0.335
Charlson Comorbidity Index (mean ± SD)	2.7 ± 2.5	1.9 ± 2.4	3.3 ± 2.8	2.7 ± 2.6	<0.001
Equivalent dose/day (mean ± SD)	102.76 ± 90.0	248.43 ± 153.5	75.47 ± 58.7	85.1 ± 60.0	<0.001
Short-acting opioid equivalent dose/day (mean ± SD)	5.7 ± 11.6	5.2 ± 18.4	6.5 ± 12.6	4.8 ± 9.8	0.262
Switched LAO after follow-up, n (%)	55 (17.9)	39 (21.9)	143 (30.4)	68 (20.1)	<0.001
Female, n (%)	207 (67.4)	125 (70.2)	207 (61.1)	304 (64.5)	0.150
Non-white, n (%)	27 (8.8)	19 (10.7)	29 (8.6)	41 (8.7)	0.860
Long-term care resident, n (%)	38 (12.4)	8 (4.5)	24 (7.1)	27 (5.7)	0.002
Non-English speaker, n (%)	9 (2.9)	4 (2.2)	13 (3.8)	8 (1.7)	0.2916
Osteoarthritis, n (%)	65 (21.2)	50 (28.1)	57 (16.8)	92 (19.5)	0.023
Fibromyalgia, n (%)	23 (7.5)	38 (21.3)	30 (8.8)	43 (9.1)	<0.0001
Back pain, n (%)	78 (25.4)	76 (42.7)	91 (26.8)	175 (37.2)	<0.0001
Neuropathic pain, n (%)	32 (10.4)	39 (21.9)	39 (11.5)	67 (14.2)	0.002
Substance abuse treatment center, n (%)	5 (1.6)	13 (7.3)	12 (3.5)	21 (4.5)	0.017
Substance abuse, n (%)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)	0.809
Substance dependence, n (%)	4 (1.3)	16 (9.0)	3 (0.9)	13 (2.8)	<0.0001

ER = extended-release; LAO = long-acting opioid.

Table 4. Demographics of Subjects with Other Pain-Related Conditions[a]

Parameter	Transdermal Fentanyl	Methadone	ER Oxycodone	ER Morphine	p Value
N = 2027	338	508	447	734	
Age, y (mean ± SD)	62.5 ± 18.9	48.9 ± 13.2	53.7 ± 15.4	52.5 ± 16.0	<0.001
Prescribers, n (mean ± SD)	2.7 ± 2.2	2.7 ± 2.2	2.7 ± 2.2	2.7 ± 2.1	0.983
Interacting drugs, n (mean ± SD)	1.67 ± 1.4	1.56 ± 1.3	1.74 ± 1.3	1.94 ± 1.5	<0.001
Charlson Comorbidity Index (mean ± SD)	0.86 ± 1.2	0.64 ± 1.1	0.83 ± 1.3	0.8 ± 1.2	0.020
Equivalent dose/day (mean ± SD)	98.4 ± 44.6	236.6 ± 247.5	67.0 ± 66.3	77.2 ± 72.2	<0.001
Short-acting opioid equivalent dose/day (mean ± SD)	4 ± 8.2	8.23 ± 9.1	5.99 ± 21.9	2.55 ± 6.0	<0.001
Switched LAO after follow-up, n (%)	90 (26.6)	102 (20.1)	258 (35.1)	100 (22.4)	<0.001
Female, n (%)	255 (75.4)	327 (64.4)	299 (66.9)	473 (64.4)	0.002
Non-white, n (%)	21 (6.2)	51 (10.0)	52 (11.6)	57 (7.8)	0.028
Long-term care resident, n (%)	65 (19.2)	8 (1.6)	34 (7.6)	37 (5.0)	<0.001
Non-English speaker, n (%)	6 (1.8)	7 (1.4)	8 (1.8)	4 (0.5)	0.180
Osteoarthritis, n (%)	147 (43.5)	170 (33.5)	177 (39.6)	269 (36.6)	0.021
Fibromyalgia, n (%)	50 (14.8)	138 (27.2)	88 (19.7)	142 (19.3)	<0.001
Back pain, n (%)	193 (57.1)	331 (65.2)	264 (59.1)	479 (65.3)	0.016
Neuropathic pain, n (%)	80 (23.7)	124 (24.4)	109 (24.4)	177 (24.1)	0.995
Substance abuse treatment center, n (%)	12 (3.6)	49 (9.6)	20 (4.5)	30 (4.1)	<0.001
Substance abuse, n (%)	1 (0.3)	6 (1.2)	2 (0.4)	0 (0.0)	0.010
Substance dependence, n (%)	9 (2.7)	43 (8.5)	11 (2.5)	21 (2.9)	<0.001

ER = extended-release; LAO = long-acting opioid.
[a]Osteoarthritis, fibromyalgia, back pain, or neuropathic pain.

A summary of outcomes measured in the cancer and noncancer subgroups is shown in Table 5. Overall, the HR observed for subjects with a cancer diagnosis were similar to estimates for the total population. However, subjects with a diagnosis of cancer in the oxycodone ER cohort had a significantly lower risk of hospitalization than those

prescribed morphine ER. Among subjects with noncancer pain diagnoses, the risk of several adverse outcomes differed qualitatively for the risk from the cancer cohort and the overall population. The transdermal fentanyl group had a statistically significant increase in the risk for ED encounter compared with the morphine ER group. The risk of experiencing a symptom of overdose was 57% higher in the methadone group compared with the morphine ER group.

Table 5. Adjusted Cox Proportional Hazard Models Among Patients with Specific Pain Diagnoses

	Cancer			Noncancer		
Parameter	HR	95% CI	p Value	HR	95% CI	p Value
ED/hospitalization[a]						
methadone	0.24	0.05 to 1.13	0.071	0.70	0.29 to 1.69	0.426
oxycodone	0.68	0.27 to 1.72	0.411	0.52	0.22 to 1.23	0.138
fentanyl	1.08	0.43 to 2.74	0.870	1.42	0.63 to 3.21	0.404
morphine (referent)						
Mortality						
methadone	0.48	0.18 to 1.23	0.127	0.78	0.29 to 2.13	0.628
oxycodone	0.74	0.46 to 1.21	0.226	0.98	0.45 to 2.14	0.961
fentanyl	0.93	0.58 to 1.49	0.768	0.89	0.43 to 1.84	0.753
morphine (referent)						
ED encounters						
methadone	0.79	0.61 to 1.04	0.089	1.13	0.91 to 1.41	0.286
oxycodone	0.88	0.71 to 1.08	0.215	0.91	0.76 to 1.10	0.327
fentanyl	0.98	0.78 to 1.22	0.837	1.27	1.02 to 1.59	0.034
morphine (referent)						
Hospitalizations						
methadone	0.85	0.61 to 1.17	0.313	1.09	0.78 to 1.52	0.630
oxycodone	0.73	0.56 to 0.94	0.014	0.87	0.67 to 1.14	0.327
fentanyl	1.06	0.82 to 1.39	0.644	1.16	0.85 to 1.59	0.356
morphine (referent)						
Opioid poisoning						
methadone	2.20	0.13 to 38.76	0.590	2.41	0.26 to 22.59	0.441
oxycodone	0.41	0.02 to 8.30	0.560	1.16	0.11 to 12.83	0.903
fentanyl						
morphine (referent)						
Overdose symptoms[b]						
methadone	1.04	0.65 to 1.66	0.881	1.57	1.03 to 2.40	0.037
oxycodone	0.77	0.52 to 1.16	0.215	1.07	0.74 to 1.53	0.731
fentanyl	1.05	0.69 to 1.60	0.826	1.10	0.72 to 1.68	0.672
morphine (referent)						
Constipation						
methadone	0.80	0.27 to 2.40	0.693	0.66	0.29 to 1.53	0.334
oxycodone	0.52	0.19 to 1.39	0.192	0.72	0.34 to 1.55	0.403
fentanyl	1.24	0.51 to 2.99	0.636	0.95	0.40 to 2.25	0.902
morphine (referent)						

ED = emergency department.
[a]Constipation, alteration of consciousness, malaise, fatigue, lethargy, respiratory failure, opioid poisoning.
[b]Alteration of consciousness, malaise, fatigue, lethargy, respiratory failure.

The authors concluded that this retrospective observational cohort study suggested that oxycodone ER may have a moderate safety advantage over morphine ER. Subjects prescribed oxycodone ER experienced significantly lower risk of the combined outcome of an ED or hospitalization for opioid-related adverse effects, as well as for the individual outcomes all-cause death, hospitalization, and constipation compared with subjects prescribed morphine ER.

SECTION 2.4: OUTCOMES STUDIES AND ECONOMIC EVALUATION SUPPORTING DATA

2.4 (b) Prospective Cost-Effectiveness Studies

Marshall et al. Economic Evaluation of Controlled-release Oxycodone vs Oxycodone-Acetaminophen for Osteoarthritis Pain of the Hip or Knee. *Am J Manag Care.* 2006;12:205-214.

The purpose of this prospective, active-controlled, randomized, naturalistic, open-label 4-month trial was to examine, in routine practice, the effectiveness and cost-effectiveness of controlled-release oxycodone (OxyContin®) compared to oxycodone/acetaminophen (Percocet®) (oxy/APAP) added to a platform of usual care in patients with moderate to severe pain from osteoarthritis (OA) of the hip or knee.

The study population consisted of patients ≥ 40 years of age with moderate to severe OA pain of the hip or knee for at least 3 months that was not adequately controlled with short-acting opioid therapy. Radiographic evidence of OA within the past 2 years also had to be shown for enrollment in the study. Four to 7 days before randomization, patients had to have taken 2 or more tablets of short-acting opioid per day (equivalent daily dose of ≥ 10 mg of oxycodone) for moderate to severe OA pain. Data were collected at the physician's office at baseline and at study termination (month 4). Patients received either controlled-release oxycodone 10 mg every 12 hours or Oxy/APAP 5/325 mg every 4 to 6 hours as needed.

For outcomes and health resource utilization data the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Likert 3.0 and the Health Utilities Index 3 (HUI3) health-related QOL (HRQOL) instruments were administered at baseline and at months 1, 2, 3, and 4 by telephone interview. For the cost-effectiveness analysis (CEA), effectiveness was measured as the proportion of "patients improved," defined per the American College of Rheumatology guidelines as having at least 20% improvement from baseline to month 4 in the WOMAC pain score. The overall HUI3 utility score was used to calculate the quality-adjusted-life-years (QALYs) for the cost-utility analysis (CUA). All health resource utilization data was collected weekly by telephone and costed using Medicare reimbursement and medications were costed using the *Drug Topics Red Book* adjusted to 2003 US dollars.

To respond to the interest of diverse audiences, analyses were evaluated from the healthcare system (HCS) and societal perspectives. The HCS perspective included costs for medications, healthcare visits, hospitalizations and emergency department visits, diagnostic tests and procedures, home healthcare services, and assistive devices. The societal perspective also included time lost from paid work and unpaid regular activities

for the patient and family and friends. The CEA was measured as cost per patient improved (over 4 months) and QALYs gained from societal and healthcare perspectives using generic oxy/APAP (base case). Uncertainty was evaluated using multiple one-way sensitivity analyses and cost-effectiveness acceptability curves (CEAC).

Five hundred thirteen patients were included in the intent-to-treat analysis; 261 patients in the oxycodone group and 252 in the oxy/APAP group. During the 4 month period with regard to health resource utilization and costs, more patients in the oxycodone group than the oxy/APAP group had used more service hours of a home health aid or nurse. Patients in the oxy/APAP group lost more hours from employment and from normal activities than patients in the oxycodone group. Time lost was the largest cost driver in the analysis from the societal perspective
(Table 1).

Table 1. Health Resource Utilization During 4 Months

Resource Utilization	Oxycodone-Acetaminophen Group (n = 252)	Oxycodone Group (n = 261)
Discrete variables, No. of resources utilized [No. of patients]		
Osteoarthritis-related emergency department visits	10 [9]	9 [7]
Osteoarthritis-related hospitalizations	0 [0]	0 [0]
Physician or nurse visits	284 [110]	287 [122]
Healthcare practitioner telephone contacts	502 [135]	815 [179]
Other healthcare professional visits	382 [59]	327 [53]
Diagnostic tests and procedures	413 [88]	324 [89]
Orthopedic devices and equipment used or purchased	381 [152]	329 [144]
Continuous variables, mean ± SD		
Home healthcare nurse for medical care, h	8 ± 2	53 ± 2
Home healthcare aide for medical care, h	70 ± 3	109 ± 5
Home healthcare aide for nonmedical care, h	1745 ± 16	1820 ± 30
Lost paid employment for family or friends, h	3.3 ± 19.7	1.7 ± 9.8
Lost paid employment for patient, h	7.5 ± 34.5	6.2 ± 31.8
Cutback on normal activities, d	33.4 ± 32.4	26.8 ± 28.3
Family or friends assisted patient, h	71.9 ± 141.7	59.2 ± 131.5

Resource use was not imputed or adjusted for the duration of time in study and was reported for all observed data regardless of patient completion status.

For patients in the oxycodone group, the total OA-related HCS costs per patient for months 1 to 4 were greater compared to the oxy/APAP group ($1951 vs $1155), driven by prescription medication costs ($751 vs $134) and home healthcare service costs ($595 vs $467). The total OA-related societal costs per patient for months 1 to 4 were lower for patients in the oxycodone group compared to the oxy/APAP group ($7379 vs 7528, p=

0.33), driven by costs associated with time lost from activities in the oxy/APAP group (Table 2).

Table 2. Osteoarthritis-related Costs During 4 Months*

Cost, $	Oxycodone-Acetaminophen (Percocet®) Group (n = 244)	Oxycodone Group (n = 241)	Difference (Oxycodone Group Minus Oxycodone-Acetaminophen Group)
Per patient			
Medications			
Prescription	134 ± 61	751 ± 420	617
Over-the-counter, herbals, constipation, mood, sleep	83 ± 110	84 ± 120	1
Physician or nurse visits	295 ± 429	371 ± 524	76
Diagnostic tests and procedures	93 ± 273	69 ± 186	−24
Osteoarthritis-related hospitalizations	0 ± 0	0 ± 0	0
Osteoarthritis-related emergency department visits	16 ± 85	11 ± 74	−5
Home healthcare services	467 ± 3405	595 ± 3235	128
Orthopedic devices and equipment from healthcare system perspective	67 ± 111	70 ± 127	3
Orthopedic devices and equipment from societal perspective	84 ± 139	86 ± 160	2
Lost time			
Paid employment for patient	157 ± 711	146 ± 705	−11
Paid employment for family or friends	72 ± 406	50 ± 249	−22
Unpaid regular activities for family or friends	1577 ± 3094	1376 ± 2814	−201
Cutback days on normal activities for patient	4550 ± 4124	3840 ± 3681	−710
Total			
From healthcare perspective	1155 ± 3434	1951 ± 3465	796
From societal perspective	7528 ± 7421	7379 ± 6741	−149

*Data are given as mean ± SD unless otherwise indicated. Costs for patients in the study for a duration less than 4 weeks were imputed using the hot-deck method of imputation.
The population used for analysis was reduced to a total of n = 485 (n = 241 for oxycodone and n = 244 for oxycodone-acetaminophen). Patients were excluded for whom no follow-up measure of the Western Ontario and McMaster Universities Index (WOMAC) pain score was available, since it was not possible to calculate the changes in WOMAC pain score.

With regard to effectiveness, the oxycodone group had a larger proportion of patients who improved compared with patients in the oxy/APAP group (62.2% vs 45.9%, $p < 0.001$). Patients in the oxycodone group also gained 0.0105 QALYs during the 4-months compared to the oxy/APAP group (p=0.17). The base-case incremental cost-effectiveness analysis from the HCS perspective showed that the incremental mean cost per patient was $796, and the difference in proportion of patients improved was 0.163. Therefore, oxycodone was more costly and more effective than oxy/APAP, with incremental cost-effectiveness ratio of $4883 per patient improved. From the societal perspective, the incremental mean cost per patient was $149 less in the oxycodone group compared with the oxy/APAP group. Therefore, oxycodone was less costly and more effective than the oxy/APAP group (Table 3).

For the base-case incremental cost-utility analysis illustrated from the HCS perspective, the incremental mean cost per patient was $796, and 0.0105 QALYs were gained in the oxycodone group compared to the oxy/APAP group. Therefore, oxycodone was more costly and more effective than oxy/APAP, with an incremental cost-utility ratio of $75,810 per QALY gained. From the societal perspective, the incremental mean cost per patient was $149 less in the oxycodone group compared with the oxy/APAP group. Since oxycodone was less costly and more effective than oxy/APAP, an incremental cost-utility ratio was not calculated (Table 3).

Table 3. Base-case Analyses From the Healthcare System (HCS) and Societal Perspectives Among 241 Patients in the Oxycodone Group and 244 Patients in the Oxycodone-Acetaminophen Group

Analysis	HCS Perspective	Societal Perspective
Total cost, $		
Oxycodone group	1951	7379
Oxycodone-acetaminophen group	1155	7528
Difference	796	−149
Proportion of patients improved		
Oxycodone group	0.622	0.622
Oxycodone-acetaminophen group	0.459	0.459
Difference	0.163	0.163
Cost per patient improved, $*	4883	Win-win
Quality-adjusted life-years (QALYs) gained		
Oxycodone group	0.1551	0.1551
Oxycodone-acetaminophen group	0.1492	0.1492
Unadjusted difference between QALYs gained	0.0059	0.0059
Difference between treatment groups in resource utilization at baseline (oxycodone group minus oxycodone-acetaminophen group)	−0.014	−0.014
Effect of this resource utilization difference on QALYs gained	−0.0046	−0.0046
Adjusted difference between QALYs gained†	0.0105	0.0105
Cost per QALY gained, $‡	75 810	Win-win

*The cost per patient improved is the incremental mean cost per patient (oxycodone group minus oxycodone-acetaminophen group) divided by the difference in the proportion of patients improved (oxycodone group minus oxycodone-acetaminophen group).
†The QALYs gained are adjusted for baseline differences.
‡The cost per QALY gained is the incremental mean cost per patient (oxycodone group minus oxycodone-acetaminophen group) divided by the incremental QALYs gained (oxycodone group minus oxycodone-acetaminophen group).

In the 1-way sensitivity analysis from the HCS perspective, the cost-effectiveness analysis results ranged from a single dominant result to $8884 per patient improved. From the societal perspective, 6 of 7 results fell in win-win quadrants (Table 4). With respect to the cost-utility analysis, the results of the 1-way sensitivity analysis from the HCS perspective, varied from oxycodone being dominated (lose-lose quadrant) to oxycodone dominating (win-win quadrant) (Table 4). Five of 7 results fell in the upper right quadrant of the cost-effectiveness plane, with incremental cost-utility ratios ranging from $26,762 to $125,048 per QALY gained. The probability that oxycodone was cost-effective was 29% at the decision threshold of $50,000 per QALY gained and 60% at the

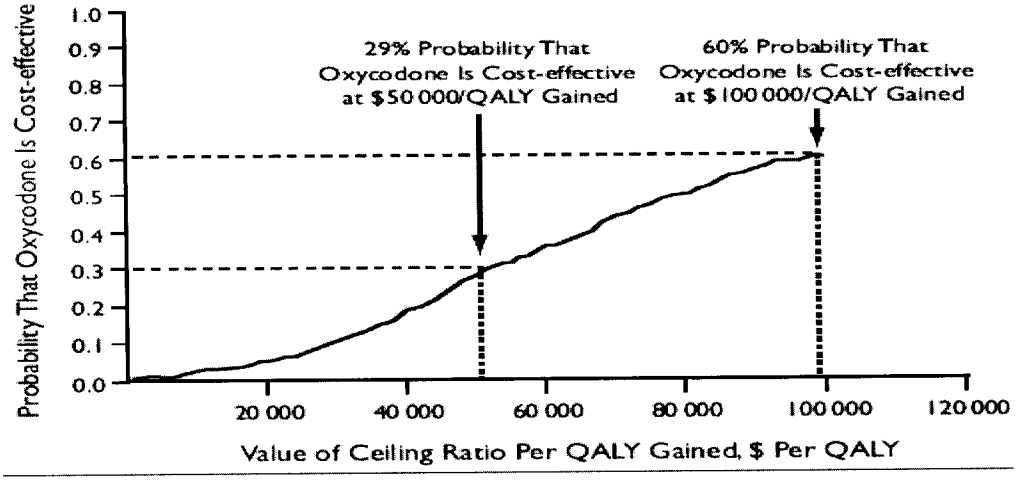
$100,000 per QALY gained (Figure 1). From the societal perspective, the cost-utility results also varied from oxycodone being dominated (lose-lose quadrant) to oxycodone dominating (win-win quadrant). Five of 7 results indicated that oxycodone dominated (win-win quadrant). The probability that oxycodone was cost-effective was 77% at the decision threshold of $50,000 per QALY gained and 84% at $100,000 per QALY gained (Figure 2).

Table 4. Cost-effectiveness and Cost-utility Analyses From the Healthcare System (HCS) and Societal Perspectives Among 241 Patients in the Oxycodone Group and 244 Patients in the Oxycodone-Acetaminophen Group: One-way Sensitivity Analysis*

	Mean Cost Difference, $		Difference in Proportion of Patients Improved	Mean Cost per Patient Improved, $			Mean Cost per QALY Gained, $	
Analysis	HCS Perspective	Societal Perspective		HCS Perspective	Societal Perspective	QALYs Gained	HCS Perspective	Societal Perspective
Base case	796	−149	0.163	4883	Win-win	0.0105	75 810	Win-win
Upper 90% CI for cost-effectiveness	796	−149	0.2364	3367	Win-win	0.0230	34 609	Win-win
Lower 90% CI for cost-effectiveness	796	−149	0.0896	8884	Win-win	−0.0020	Lose-lose	74 500†
Total cost for upper 90% CI for cost-effectiveness	1313	912	0.163	8055	5595	0.0105	125 048	86 857
Total cost for lower 90% CI for cost-effectiveness	281	−1210	0.163	1724	Win-win	0.0105	26 762	Win-win
Total cost using brand oxycodone-acetaminophen	−122	−1068	0.163	Win-win	Win-win	0.0105	Win-win	Win-win
Total cost using 50% physician visits and 50% nurse visits	763	−183	0.163	4681	Win-win	0.0105	72 667	Win-win
Total cost including health resource utilization associated with adverse effects of osteoarthritis treatment	803	−143	0.163	4926	Win-win	0.0105	76 476	Win-win

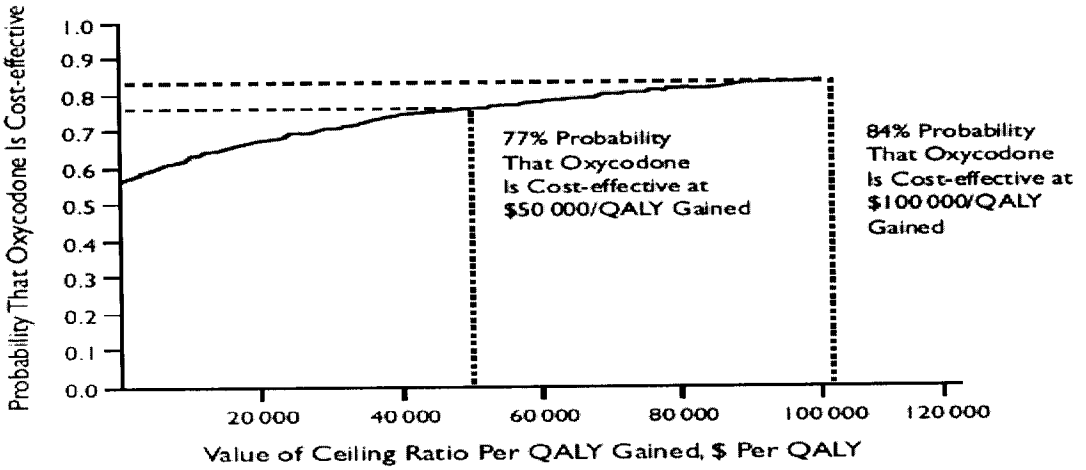
*Win-win indicates oxycodone is more effective and less costly than oxycodone-acetaminophen; and lose-lose, oxycodone is less effective and more costly than oxycodone-acetaminophen.
†This cost-utility estimate is for oxycodone-acetaminophen compared with oxycodone.
QALYs indicates quality-adjusted life-years; CI, confidence interval.

Figure 1. Cost-effectiveness Acceptability Curve for the Cost-utility Analysis From the Healthcare System Perspective



QALY indicates quality-adjusted life-year.

Figure 2. Cost-effectiveness Acceptability Curve for the Cost-utility Analysis From the Social Perspective



QALY indicates quality-adjusted life-year.

Overall, the study found that from a societal perspective, controlled-release oxycodone was more effective and less costly than oxy/APAP. From the healthcare perspective, controlled-release oxycodone (compared with generic oxy/APAP) fell within the acceptable range of cost-effectiveness between $50,000 and $100,000 per QALY gained.

5.0 SUPPORTING INFORMATION

5.1 References

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